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Long-Term Treatment of Refractory Thrombocytopenia in a Patient With Wiskott-Aldrich Syndrome With Vincristine, Immunoglobulin, and Methylprednisolone

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We report a child with Wiskott-Aldrich syndrome with severe, refractory, symptomatic thrombocytopenia who achieved an excellent response to combination therapy with vincristine 1.5 mg/m² × 1 day, intravenous immunoglobulin 1 g/kg × 3 days, and methylprednisolone 25 mg/kg × 3 days (VIM) for 7 years after failing multiple treatments. He did not have a histocompatible donor for bone marrow transplantation. When the patient ceased to respond to this regimen, he was rescued with pulse dexamethasone. Vincristine, immunoglobulin, and methylprednisolone might serve as a novel treatment option for the patient with refractory thrombocytopenia. Our patient had a sustained remission of symptomatic thrombocytopenia without toxicity. Furthermore, pulse dexamethasone might be an alternative treatment option to which patients with Wiskott-Aldrich syndrome may respond. Am. J. Hematol. 62:183–185, 1999. © 1999 Wiley-Liss, Inc.

Key words: Wiskott-Aldrich syndrome; thrombocytopenia therapy

INTRODUCTION

Wiskott-Aldrich syndrome (WAS) is a rare X-linked recessive condition which classically consists of thrombocytopenia, immunodeficiency, and eczema [1–4]. Recently, the gene responsible for WAS has been isolated, mapped to Xp11.22 and found to encode a 502 amino acid protein (WAS protein) [5]. To date, 12 unique mutations in the WAS gene have been identified [6]. The complete function of this protein remains to be elucidated, but it appears to be involved in lymphoid cell signaling [7]. Affected males also have a propensity for malignancies in the second decade of life, with the majority being lymphomas and leukemias [8]. The syndrome is fatal, as many patients die either from bleeding or succumb to severe infections during the first decade of life. Those that survive into their teenage years most often die from malignancies [8]. The only potential cure is bone marrow transplantation (BMT) when a histocompatible donor is available [9,10].

The mechanism of thrombocytopenia in WAS is not completely understood. Several studies have suggested that the thrombocytopenia is due to increased platelet destruction because the number of megakaryocytes in the bone marrow of WAS patients is normal [11] and they demonstrate increased platelet-associated immunoglobulin G [12,13]. In addition, some patients respond to splenectomy [12] and immunomodulatory therapies (IVIG and steroids) [4]. In contrast, patients with WAS also have a low number of reticulated platelets suggesting decreased production [14]. Furthermore, WAS platelets are extremely small and display impaired aggregation increasing the risk of bleeding. The reason for the impaired aggregation is likely due to decreased expression of GPIIb/IIIa and decreased up-regulation in response to thrombin [14].

We report a patient with refractory thrombocytopenia, who was not a candidate for BMT due to the lack of a histocompatible donor, and who demonstrates a sustained response to vincristine, immunoglobulin, and methylprednisolone (VIM) and, subsequently, to cyclic pulse dexamethasone.

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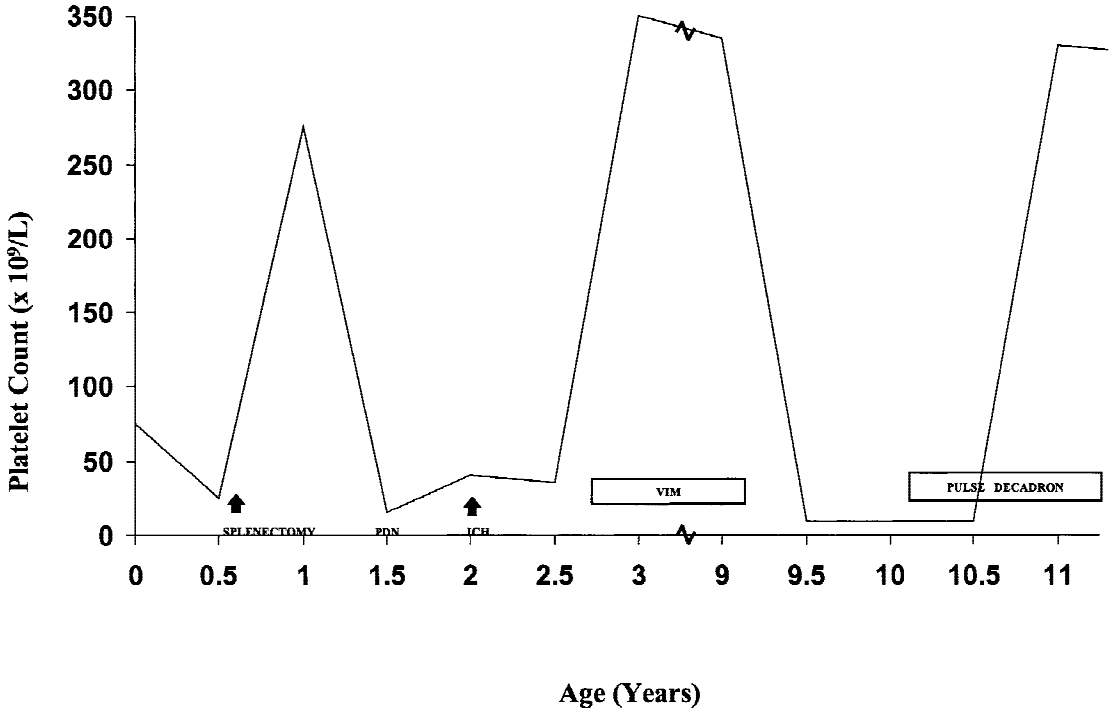

Fig. 1. Graphical representation of platelet count during different phases of treatment. PDN, prednisone; ICH, intracranial hemorrhage; VIM, vincristine-IVIG-methylprednisolone.

CASE REPORT

A six-month-old boy was diagnosed with WAS after presenting with gingival bleeding, easy bruisability, and eczema. Genetic evaluation was not available at that time. Thus, his diagnosis was based on clinical symptoms and laboratory evidence including small platelets (MPV-4.8fL), absent isohemagluttinins, and depressed T-cell responses to mitogens. Due to persistent, symptomatic thrombocytopenia (platelet counts $< 30 \times 10^9$/l) manifested as mucocutaneous hemorrhage, he underwent a splenectomy at the age of 9 months.

At 15 months, when his thrombocytopenia (platelet count 20×10^9/l) and bleeding recurred, prednisone therapy was started at 2 mg/kg/day without an appreciable change in the platelet count or symptoms.

At 20 months, a left parietal hemorrhagic infarct occurred with a platelet count of 50×10^9/l. His residual neurologic deficits included a right hemiparesis. Thus, it was decided to keep his platelet count above 100×10^9/l. Due to the lack of a histocompatible donor, BMT was not an option. The following treatment modalities were tried without a clinically significant rise in the platelet counts (platelet counts $< 30 \times 10^9$/l): intravenous immunoglobulin (IVIG) 1 g/kg × 3 doses monthly; intravenous methylprednisolone at doses from 15 mg/kg to 30 mg/kg × 3 doses every 2 to 4 weeks; vinblastine 6mg/m^2 once per month for two doses.

At the age of 30 months, the innovative combination of VIM (vincristine 1.5 mg/m^2 × 1 day, IVIG 1 g/kg × 3 days, and methylprednisolone 25 mg/kg × 3) days was tried. Remarkably, his platelet count rose to over 100×10^9/l in 3 weeks. After two cycles, his platelet count increased to 220×10^9/l. He continued to receive this combination monthly for 7 years, and his platelet count dropped below 50×10^9/l on only two occasions in association with an acute infection.

After 7 years of treatment with VIM, he suddenly failed to respond and his platelet counts fell and remained persistently below 10×10^9/l. Despite administering treatments every 3 weeks and a 4 week trial of cyclosporin 4.5 mg/kg/day, his platelet count remained below 10×10^9/l. He suffered from numerous episodes of epistaxis, gingival bleeding, and hematuria requiring platelet transfusions. At this time, he was started on pulse dexamethasone at 25 mg/m^2 × 4 days every 4 weeks. After course 4 and 5 of dexamethasone, the platelet count increased to 194×10^9/l and 250×10^9/l, respectively. His response to dexamethasone was briefly attenuated during an episode of *Staphylococcus epidermidis* sepsis. Since then, he has been on dexamethasone pulse every 3 weeks. His platelet count has remained above 200×10^9/l for 2 years even in the presence of active cytomegalovirus infection (see Fig. 1).

DISCUSSION

We report here the case of a patient with classic WAS, ineligible for BMT, whose thrombocytopenia was suc-

cessfully treated with VIM, and subsequently pulse dexamethasone. The thrombocytopenia in WAS can be extremely difficult to treat. In fact, bleeding is a the most common cause of death during the first decade of life, and 4% to 10% of all WAS patients in one survey died from bleeding [4]. Various approaches have been used; IVIG, steroids, other immunosuppressive agents, and splenectomy being the most common. BMT remains the only definitive treatment, which for this patient was not possible.

There are a number of interesting observations to be made from this case. First, VIM as a combination has not been previously reported, and may represent a treatment option for refractory thrombocytopenia in patients with WAS in which BMT is not possible. In addition, our patient's excellent response to VIM is remarkable for its duration and lack of toxicity. Specifically, there was no evidence of growth failure, cataracts, osteoporosis, hypertension, aseptic meningitis, serum sickness, nephropathy, seizures, SIADH, or neuropathy. There were no acute toxicities. This combination of agents had not been previously used to treat refractory thrombocytopenia. Recently, a similar regimen (with the addition of danazol) was used by Scaradavou [15] to treat patients with refractory Evan's syndrome with some success. Figueroa described the use of combination chemotherapy for adults with refractory chronic ITP [16].

The second interesting observation is this patient's response to pulse dexamethasone. Anderson [17] first reported the success of this approach in adults and subsequently, Adams [18] reported its success in children. This early optimism has been tempered by several recent reports demonstrating the lack of a long-term response. In a study by Kuhne [19], only one of 11 patients achieved a complete and durable response (platelet count $> 150 \times 10^9$/l), whereas 3 achieved a partial response (platelet count between 50 and 150×10^9/l). Borgna-Pignatti [20] demonstrated a complete and durable response in only 5 of 17 patients studied. As reported by Andersen [17], the response to cyclic dexamethasone may take several months, especially in splenectomized patients.

In conclusion, we report a patient with WAS who was not a candidate for BMT, who had a remarkable 7 year response to monthly combination therapy of VIM. The patient is currently is responding to monthly pulse dexamethasone therapy for 2 years. Thus, these two regimens might be successful treatment options for other patients with refractory thrombocytopenia.

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